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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344

32650 7590 03/24/2004

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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,39-49,51-53,55-59,61 and 63-65* is/are pending in the application.

4a) Of the above claim(s) *39-41,43,52,53,59 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,42,44-49,51,55-58,61,63 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 12-24-03.

Claims 37, 39-49, 51-53, 55-59, 61 and 63-65 are pending in the instant application. Claims 39-41, 43, 52, 53, 59 and 64 have been withdrawn from consideration as being drawn to a non-elected invention.

Election/Restrictions

This application contains claims 39-41, 43, 52, 53, 59 and 64, drawn to an invention nonelected with traverse in Paper No. 3-30-00. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments and Amendments

Priority

Applicants argue that appropriate support for claimed priority of May 23, 1991 has been provided for the instant invention because the priority document states that oligonucleotides may be formulated in a pharmaceutical formulation, and that one skilled in the art would assume that such formulations would provide support for aerosolized formulations of oligonucleotides, and would also include the newly added limitations "wherein the aerosolized composition comprises liquid particles or solid particles." Contrary to Applicant's assertions, inadequate support has been provided in the instant disclosure, and in the priority documents claimed, for these limitations, as

well as for lung delivery methods of oligonucleotides. The priority date awarded for the instantly claimed invention is May 20, 1999.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Applicant's arguments with respect to claims 37, 42, 44-49, 51, 54-58 and 61 under 35 U.S.C. 102(e) as being anticipated by Unger et al have been considered but are moot in view of the new ground(s) of rejection set forth below.

Applicant's arguments with respect to claim 63 under 35 U.S.C. 103(a) as being unpatentable over Unger et al in view of Bennett et al have been considered but are moot in view of the new ground(s) of rejection set forth below.

Maintained Rejections

Claims 37, 42, 44-49, 51, 55-58, 61, 63 and 65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-34, 36, 39, 43-46, 50, 52, 53 and 55-83 of copending Application No. 09/315,581 for the reasons of record set forth in the Office action mailed 8-25-03.

No arguments have been made addressing this rejection.

Claims 37, 42, 44-49, 51, 55-58, 61, 63 and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons of record set forth in the Office action mailed 8-25-03.

The metes and bounds of claim 37, lines 4-7, and claim 54, lines 3-6, which recite the negative limitation of at least one sugar moiety of at least one nucleoside unit ... is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage is not a phosphodiester or a phosphorothioate linkage, cannot be determined.

Applicant's arguments filed 12-24-03 have been fully considered but they are not persuasive. Applicants argue that the language of the claims is clear to those of skill in the art and, in addition, applicant provides various examples of modified oligonucleotides that would be encompassed by the claimed invention. Contrary to applicant's assertions, the claimed subject matter comprising an oligonucleotide wherein at least one of the sugar moieties of the oligonucleotide is other than a 2'-deoxyribofuranosyl sugar moiety, or wherein the oligonucleotide contains at least one internucleotide linkage that is other than a phosphodiester or a phosphorothioate linkage, read on a myriad of oligonucleotides, the metes and bounds of which cannot be determined from the language of the claims.

Claims 37, 42, 44-49, 51, 55-58, 61, 63 and 65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the Office action mailed 8-25-03.

Applicant's arguments filed 12-24-03 have been fully considered but they are not persuasive. Applicants argue that adequate written description has been provided in the instant disclosure to describe the broad genus comprising antisense oligonucleotides comprising at least one sugar moiety of at least one nucleoside unit that is not a 2'-deoxyribofuranosyl sugar moiety

or at least one internucleotide linkage that is not a phosphodiester or a phosphorothioate linkage. Applicants argue further that since the claims read on methods of delivery, the written description requirement for the compounds claimed within the methods invention is inappropriate and that no written description requirement exists.

Contrary to applicants' assertions, the genus comprising antisense oligonucleotides comprising at least one sugar moiety of at least one nucleoside unit that is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage that is not a phosphodiester or a phosphorothioate linkage is very broad and no concise common structural attributes have been set forth to adequately describe this amorphous genus. In addition, the fact that this amorphous and very broad genus appears in a method claim does not preclude the requirement to adequately describe the genus of compounds to be delivered in the methods claims. The subject matter claimed, in whatever context it appears, must be adequately described to satisfy the written restriction requirement. This requirement for adequate written description has been set forth in 35 U.S.C. 112, first paragraph (emphasis added):

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Interim written description guidelines were provided in 1998 but the USPTO, prompted by *Regents of the University of California v. Eli Lilly Co.*, and reconcile *Eli Lilly* with *In re Killer*. The Notice and Request for Comments were published in 64 FR 71427 on December 21, 1999 and 1231 OG 123 on February 29, 2000. The comment period closed on March 22, 2000.

Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37, 42, 44-49, 51, 55-58, 61, 63 and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The newly added limitations (aerosolized compositions comprising liquid or solid particles, penetration enhancers, as well as the limitations comprising at least one sugar moiety of at least one nucleoside unit that is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage is not a phosphodiester or a phosphorothioate linkage) appear to constitute new matter. Please provide support for these added limitations in the instant specification and/or the claimed priority documents.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 37, 42, 44-49, 51, 55-58 and 61 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Debs et al.

Debs et al (USPN 5,858,784) teach a medical devices and methods for administration of antisense nucleic acids to the lungs of a mammal, which antisense is not a 2'-deoxyribofuranosyl sugar moiety or a phosphorothioate linkage, and wherein the aerosolized composition comprises liquid or solid particles or powder, a pharmaceutically acceptable carrier including sterile, pyrogen free water, or saline solution (see entire document, especially col. 6, col. 14 – col. 26; claim 11).

Claims 37, 42, 44-49, 51, 54-58 and 61 are rejected under 35 U.S.C. 102(e) as being anticipated by Debs et al.

Debs et al (USPN 6,468,798) teach a medical devices and methods for administration of antisense nucleic acids to the lungs of a mammal, which antisense is not a 2'-deoxyribofuranosyl sugar moiety or a phosphorothioate linkage, and wherein the aerosolized composition comprises liquid or solid particles or powder, a pharmaceutically acceptable carrier including sterile,

pyrogen free water, or saline solution (see entire document, especially col. 6, col. 14 – col. 26; claims 1-33).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over Debs et al in view of Bennett et al.

The claimed invention is drawn to a method of administration of an antisense oligonucleotide of SEQ ID NO: 1, comprising aerosolizing the antisense and introducing the antisense into the lungs of a subject, wherein the sugar moiety of at least one nucleoside unit of the antisense is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense is not a phosphorothioate or phosphodiester linkage.

Debs et al (USPN 6,468,798) are relied upon as cited in the 102 rejection above.

Debs et al do not teach the administration of antisense of SEQ ID NO: 1.

Bennett et al (USPN 5514,788) teach methods of administration of antisense oligonucleotide of SEQ ID NO: 1, for inhibition of target gene ICAM-1 expression (See SEQ ID NO: 22; col. 7-8; col. 23-27).

It would have been obvious to one of ordinary skill in the art to administer the antisense oligonucleotide comprising SEQ ID NO: 1 to inhibit target gene expression because the design and targeting of ICAM-1 had been taught previously by Bennett et al using SEQ ID NO: 1. One of ordinary skill in the art would have been motivated to administer this antisense in nebulized form for lung delivery because Debs teaches the ability to deliver nebulized antisense oligonucleotides to the lungs of subjects and ICAM-1 has been taught to be involved in various inflammatory processes, and one would be motivated to deliver antisense targeting ICAM-1 to the lungs to diminish inflammatory processes occurring in the lungs due to overexpression of ICAM-1 One of ordinary skill in the art would have expected that this antisense oligonucleotide is successfully delivered to lung cells because Unger teaches the ability to deliver aerosolized antisense oligonucleotides to target cells in the lungs.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art.

Conclusion

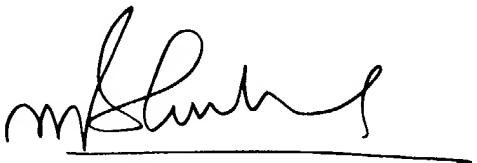
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John

LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ
3-17-04